NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Anoro Ellipta powder for inhalation, Umeclidinium (as bromide) (62.5 mcg)/vilanterol (as trifenatate) (25 mcg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each delivered dose (the dose leaving the mouthpiece of the inhaler) contains 55 micrograms umeclidinium (equivalent to 65 micrograms of umeclidinium bromide) and 22 micrograms vilanterol (as trifenatate).

Excipient with known effect:

Each delivered dose contains approximately 25 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Powder for Inhalation

White powder in a light grey inhaler (Ellipta) with a red mouthpiece cover and a dose counter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Anoro Ellipta is indicated as a long-term once daily maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

4.2 Dose and method of administration

Dose

Adults

The recommended and maximum dose is one inhalation of Anoro Ellipta (62.5/25 micrograms) once daily, at the same time of the day each day.

Special populations

Elderly population

No dosage adjustment is required in patients over 65 years (see section 5.2. Pharmacokinetic properties – Special Patient Populations- *Elderly*).

Renal impairment

No dosage adjustment is required in patients with renal impairment (see section 5.2. Pharmacokinetic properties – Special Patient Populations- *Renal impairment*).

Hepatic impairment

No dosage adjustment is required in patients with mild or moderate hepatic impairment. Anoro Ellipta has not been studied in patients with severe hepatic impairment (see section 5.2. Pharmacokinetic properties – Special Patient Populations- *Hepatic impairment*).

Method of administration

Anoro Ellipta is for oral inhalation use only.

For instructions on the use and handling of this medicine, please refer to section 6.6 Special precautions for disposal and other handling.

4.3 Contraindications

Anoro Ellipta is contraindicated in patients with severe milk-protein allergy or who have demonstrated hypersensitivity to either umeclidinium, vilanterol trifenatate or any of the excipients

4.4 Special warnings and precautions for use

The use of Anoro Ellipta has not been studied in patients with asthma, and is not recommended in this patient population.

Anoro Ellipta is intended for the long-term maintenance treatment of COPD. It should not be used for the relief of acute symptoms, i.e. as rescue therapy for the treatment of acute episodes of bronchospasm. Acute symptoms should be treated with an inhaled short-acting bronchodilator. Increasing use of short-acting bronchodilators to relieve symptoms indicates deterioration of control and patients should be reviewed by a physician.

As with other inhalation therapies, administration of Anoro Ellipta may produce paradoxical bronchospasm that may be life threatening. Treatment with Anoro Ellipta should be discontinued if paradoxical bronchospasm occurs and alternative therapy instituted if necessary.

Cardiovascular effects, such as cardiac arrhythmias e.g. atrial fibrillation and tachycardia, may be seen after the administration of sympathomimetic agents and muscarinic receptor antagonists, including Anoro Ellipta. Therefore, Anoro Ellipta should be used with caution in patients with severe cardiovascular disease.

Consistent with its antimuscarinic activity, Anoro Ellipta should be used with caution in patients with narrow-angle glaucoma or urinary retention.

Special populations

Paediatric Use:

The use in children is not relevant in a COPD indication.

Use in the Elderly:

There are no special precautions for use in the elderly.

4.5 Interaction with other medicines and other forms of interaction

Clinically significant drug interactions mediated by umeclidinium and vilanterol at clinical doses are considered unlikely due to the low plasma concentrations achieved after inhaled dosing.

Interaction with beta-blockers

Beta-adrenergic blockers may weaken or antagonise the effect of $beta_2$-agonists, such as vilanterol trifenatate. Concurrent use of either non-selective or selective beta-adrenergic blockers should be avoided unless there are compelling reasons for their use.

Interaction with CYP3A4 inhibitors

Vilanterol trifenatate is cleared by CYP3A4 mediated extensive first-pass metabolism in the gastrointestinal tract and in the liver.

Co-administration with the strong CYP3A4 inhibitor ketoconazole (400 mg) increased mean vilanterol $AUC_{(0-t)}$ and C_{max}, 65% and 22% respectively. The increase in vilanterol exposure was not associated with an increase in beta-agonist related systemic effects on heart rate, blood potassium or QT interval (corrected using the Fridericia method).

Care is advised when co-administering with strong CYP3A4 inhibitors (e.g. ketoconazole) as there is potential for an increased systemic exposure to vilanterol trifenatate, which could lead to an increase in the potential for adverse reactions (see section 5.2. Pharmacokinetic properties).

Interaction with P-glycoprotein inhibitors

Both umeclidinium and vilanterol are substrates of P-glycoprotein (P-gp). The effect of the moderate P-gp transporter inhibitor verapamil (240 mg once daily) on the steady-state pharmacokinetics of umeclidinium and vilanterol was assessed in healthy volunteers. No effect of verapamil was observed on umeclidinium or vilanterol Cmax. An approximately 1.4-fold increase in umeclidinium AUC was observed with no effect on vilanterol AUC. Based on the magnitude of these changes, no clinically relevant drug interaction is expected when umeclidinium bromide/vilanterol is co-administered with P-gp inhibitors.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well-controlled trials of umeclidinium/vilanterol or its individual components, umeclidinium and vilanterol, in pregnant women. Studies in animals have shown reproductive toxicity after inhaled administration of vilanterol.

Anoro Ellipta should be used during pregnancy only if the expected benefit to the mother justifies the potential risk to the foetus.

Breast-feeding

It is unknown whether umeclidinium or vilanterol are excreted in human milk. However, other $beta_2$-agonists are detected in human milk. A risk to breastfed newborns/infants cannot be excluded.

A decision must be made whether to discontinue breastfeeding or to discontinue Anoro Ellipta therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman

Fertility

There are no data on the effects of umeclidinium/vilanterol on human fertility. Animal studies indicate no effects of umeclidinium or vilanterol trifenatate on fertility.

4.7 Effects on ability to drive and use machines

Umeclidinium/ vilanterol has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The safety profile of umeclidinium/vilanterol is based on 2,454 patients with COPD who received doses of umeclidinium/vilanterol 62.5/25 micrograms or greater for up to one year during clinical studies. This includes 1,124 patients who received umeclidinium/vilanterol 62.5/25 micrograms and 1,330 patients who received umeclidinium/vilanterol 125/25 micrograms, both once daily.

Tabulated summary of adverse reactions

Adverse drug reactions (ADRs) are listed below by MedDRA system organ class and by frequency. The following convention has been used for the classification of adverse reactions:

Very common: ≥1/10

Common: ≥1/100 to <1/10

Uncommon: ≥1/1000 to <1/100

Rare: ≥1/10000 to <1/1000

Very rare: <1/10000

MedDRA **System organ class**	**Adverse reaction(s)**	**Frequency**
Infections and infestations	Urinary tract infection	Common
	Sinusitis	Common
	Nasopharyngitis	Common
	Pharyngitis	Common
	Upper respiratory tract infection	Common
Cardiac Disorders	Atrial Fibrillation	Uncommon
	Supraventricular tachycardia	Uncommon

MedDRA System organ class	Adverse reaction(s)	Frequency
	Tachycardia	Uncommon
Respiratory, Thoracic and Mediastinal Disorders	Cough Oropharyngeal pain	Common Common
Gastrointestinal Disorders	Constipation Dry mouth	Common Common

Clinical trial data

6 month studies

Error! Reference source not found. shows all adverse events that occurred with a frequency of greater than 1% in groups receiving umeclidinium/vilanterol 62.5/25 micrograms from four 24-week well-controlled studies (DB2113361, DB2113373, DB2113360 and DB2113374) where the rates in either of the groups receiving umeclidinium/vilanterol exceeded placebo by greater than 1%.

Table 1 Adverse Events with >1% Incidence and greater than Placebo by 1% with umeclidinium/vilanterol 62.5/25 micrograms in Subjects with COPD

Adverse Event	Placebo (n=555) n (%)	ANORO ELLIPTA 62.5/25 mcg (n=842) n (%)	ANORO ELLIPTA 125/25 mcg (n=832) n (%)	Umeclidinium 62.5 mcg (n=418) n (%)	Umeclidinium 125 mcg (n=629) n (%)	Vilanterol 25 mcg (n=1,034) n (%)	Tiotropium bromide 18 mcg (n=423) n (%)
Respiratory, Thoracic and Mediastinal Disorders							
Cough	23 (4)	18 (2)	44 (5)	16 (4)	29 (5)	37 (4)	11 (3)
Infections and Infestations							
Pharyngitis	2 (<1)	16 (2)	5 (<1)	6 (1)	7 (1)	16 (2)	5 (1)
Gastrointestinal Disorders							
Dry mouth	2 (<1)	4 (<1)	14 (2)	3 (<1)	5 (<1)	6 (<1)	7 (2)
Constipation	1 (<1)	12 (1)	9 (1)	1 (<1)	7 (1)	6 (<1)	3 (<1)

Studies DB2113361, DB2113373, DB2113360, and DB2113374

Incidence boundaries are applied prior to rounding percentages for presentation in the table.

12-month study

In a long-term safety study (DB2113359), 335 subjects were treated for up to 12 months with umeclidinium/vilanterol 125/25 micrograms or placebo. The demographic and baseline characteristics of the long-term safety study were similar to those of the placebo-controlled efficacy studies. Adverse events that occurred with a frequency of greater than 1% in the group receiving umeclidinium/vilanterol 125/25 micrograms and exceeded

placebo by greater than 1% reported in this study were: back pain (umeclidinium/vilanterol 4%, placebo 3%), cough (umeclidinium/vilanterol 3%, placebo <1%), urinary tract infection (umeclidinium/vilanterol 2%, placebo 0%), abdominal pain (umeclidinium/vilanterol 2%, placebo 0%), pleuritic pain (umeclidinium/vilanterol 1%, placebo 0%), and diabetes mellitus (umeclidinium/vilanterol 1%, placebo 0%).

Post-marketing data

MedDRA **System organ class**	**Adverse reaction(s)**	**Frequency**
Immune system disorders	Hypersensitivity reactions including: Rash Anaphylaxis, angioedema, and urticaria	 Uncommon Rare
Psychiatric disorders	Anxiety	Uncommon
Nervous system disorders	Tremor Dysgeusia Headache	Uncommon Uncommon Rare
Eye disorders	Vision blurred Glaucoma Intraocular pressure increased Eye pain	Rare Rare Rare Rare
Cardiac disorders	Palpitations	Uncommon
Respiratory, Thoracic and Mediastinal Disorders	Paradoxical bronchospasm Dysphonia	Rare Rare
Musculoskeletal and connective tissue disorders	Muscle spasms	Uncommon
Renal and urinary disorders	Urinary retention Dysuria	Rare Rare

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via: http://nzphvc.otago.ac.nz/reporting

4.9 Overdose

Symptoms and signs

An overdose of Anoro Ellipta will likely produce signs and symptoms due to the individual components' actions, consistent with the known inhaled muscarinic antagonist adverse effects (e.g. dry mouth, visual accommodation disturbances and tachycardia) and those seen with overdose of other beta$_2$-agonists (e.g. tremor, headache and tachycardia).

Treatment

If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

For advice on the management of information on the management of overdose, please contact the New Zealand National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMOCOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for obstructive airway diseases, adrenergics in combination with anticholinergics, ATC code: R03AL03

Mechanism of action

Anoro Ellipta is a combination inhaled long-acting muscarinic receptor antagonist/long-acting beta$_2$-adrenergic agonist (LAMA/LABA). Following inhalation both compounds act locally on airways to produce bronchodilation by separate mechanisms.

Umeclidinium

Umeclidinium is a long acting muscarinic receptor antagonist (also referred to as an anticholinergic). It is a quinuclidine derivative that is a muscarinic receptor antagonist with activity across multiple muscarinic cholinergic receptor subtypes. Umeclidinium exerts its bronchodilatory activity by competitively inhibiting the binding of acetylcholine with muscarinic acetylcholine receptors on airway smooth muscle. It demonstrates slow reversibility at the human M3 muscarinic receptor subtype in vitro and a long duration of action in vivo when administered directly to the lungs in pre-clinical models.

Vilanterol

Vilanterol is a selective long-acting, beta$_2$-adrenergic receptor agonist (beta$_2$-agonist).

The pharmacologic effects of beta$_2$-agonists, including vilanterol trifenatate, are at least in part attributable to stimulation of intracellular adenylate cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

Pharmacodynamic effects

Improvement in lung function over placebo was seen at 15 minutes (the first time point assessed after dosing) and was maintained over 24 hours. In one placebo controlled clinical efficacy study, umeclidinium/vilanterol 62.5/25 micrograms increased FEV_1 after the first dose on Day 1 with an improvement compared to placebo of 112 ml [95% CI=96 ml to 129 ml] at 15 minutes following administration. The change from baseline to peak FEV_1 during 0-6 hours post-dose at Day 1 and Week 24 was 273 ml and 320 ml respectively for umeclidinium/vilanterol 62.5/25 micrograms compared with 106 ml and 96 ml (Week 24) for placebo. There was no evidence for tachyphylaxis to the bronchodilator effect after repeated dosing of umeclidinium/vilanterol over time.

Cardiovascular effects

The effect of umeclidinium/vilanterol on the QT interval was evaluated in a placebo and moxifloxacin controlled QT study involving once daily administration of umeclidinium/vilanterol 125/25 micrograms or 500/100 micrograms for 10 days in 103 healthy volunteers. The maximum mean difference in prolongations of QT interval (corrected using the Fridericia method, QTcF) from placebo after baseline-correction was 4.3 (90% CI=2.2 to 6.4) milliseconds seen 10 minutes after administration with umeclidinium/vilanterol 125/25 micrograms and 8.2 (90% CI=6.2 to 10.2) milliseconds seen 30 minutes after administration with umeclidinium/vilanterol 500/100 micrograms. No clinically relevant effect on prolongation of QT interval (corrected using the Fridericia method) was observed.

In addition, no clinically significant effects of umeclidinium/vilanterol on cardiac rhythm were observed on 24-hour Holter monitoring in 108 patients with COPD treated for up to 6 months (of whom 53 patients received umeclidinium/vilanterol 62.5/25 micrograms and 55 patients received umeclidinium/vilanterol 125/25 micrograms once daily), and in a further 226 patients who received umeclidinium/vilanterol 125/25 micrograms once daily for up to 12 months

Clinical efficacy and safety

The safety and efficacy of umeclidinium/vilanterol administered once daily were evaluated in eight Phase III clinical studies in adult patients with a clinical diagnosis of COPD. Five studies were 6-month efficacy studies, two of these studies evaluated umeclidinium/vilanterol 62.5/25 micrograms and umeclidinium/vilanterol 125/25 micrograms (DB2113360 and DB2113374), two studies evaluated umeclidinium/vilanterol 62.5/25 micrograms (DB2113373 and ZEP117115) and one study evaluated umeclidinium/vilanterol 125/25 micrograms (DB2113361). In addition, there were two 12-week exercise endurance studies that included both umeclidinium/vilanterol 62.5/25 micrograms and umeclidinium/vilanterol 125/25 micrograms (DB2114417 and DB2114418) and one study (DB2113359) that evaluated the safety of umeclidinium/vilanterol 125/25 micrograms administered over a 12-month treatment period.

Efficacy results for umeclidinium/vilanterol 62.5/25 micrograms are presented below.

Placebo Controlled Studies

In one 6-month placebo-controlled study (DB2113373) umeclidinium/vilanterol 62.5/25 micrograms demonstrated a statistically significant improvement in lung function as defined by change from baseline trough FEV_1 (primary end point) compared with placebo. At Week 24, umeclidinium/vilanterol 62.5/25 micrograms increased trough FEV_1 by 167 ml (95% CI=128 ml to 207 ml, $p<0.001$) compared with placebo. Umeclidinium/vilanterol 62.5/25 micrograms demonstrated greater improvements from baseline in weighted mean FEV_1 over 0-6 hours post-dose at Week 24 (secondary endpoint) compared with placebo (242 ml [95% CI=202 ml to 282 ml]. Bronchodilatory effects with umeclidinium/vilanterol

62.5/25 micrograms compared with placebo were evident after the first day of treatment and were maintained over the 24 week treatment period.

Umeclidinium/vilanterol 62.5/25 micrograms demonstrated clinically meaningful improvements compared with placebo in breathlessness (evaluated by TDI focal score), health related quality of life (as assessed by Saint George's Respiratory Questionnaire [SGRQ total score]) and rescue use throughout the study period (see *Table 2*).

Table 2. Symptom relief from 6 months treatment duration

Variable	Treatment		
	Anoro Ellipta 62.5/25 micrograms OD (n= 413)	Placebo (n=280)	Improvement over Placebo (95% CI) p-value
TDI Focal Score			
Mean (units)	2.4	1.2	1.2 (0.7,1.7) <0.001
Percentage of patients who achieved MCID[a, b]	58% (226/389)	41% (106/260)	2.0[c] (1.5,2.8)
SGRQ Total Score			
Mean change from baseline (units)	-8.07	-2.56	-5.51 (-7.88, -3.13)
Percentage of patients who achieved MCID[b, d]	49% (188/381)	34% (86/254)	2.0[c] (1.4,2.8)
Use of rescue medication			
Mean change from baseline in mean number of puffs/day of rescue medication use	-2.3	-1.4	-0.8 (-1.3,-0.3)
Mean percentage of days with no rescue medication use	36.1%	21.7%	n/e

Abbreviations: CI= confidence interval; MCID= minimum clinically important difference; n= number receiving treatment; n/e= not evaluated; OD= once daily; SGRQ= Saint George's Respiratory Questionnaire TDI= Transition Dyspnoea Index.
a. MCID of at least 1 unit TDI Focal Score
b. Percentage of subjects with data at Week 24
c. Odds ratio, ratio of the odds of achieving the MCID vs. not achieving the MCID on umeclidinium/vilanterol 62.5/25 micrograms compared to placebo.
d. MCID of at least -4 units change from baseline in SGRQ Score

Treatment with umeclidinium/vilanterol resulted in a statistically significant 50% reduction in risk of a moderate/severe COPD exacerbation (based on analysis of time to first exacerbation) compared with placebo (Hazard Ratio 0.5; 95% CI: 0.3, 0.8; p=0.004) where the majority of patients reported no COPD exacerbations requiring oral/systemic corticosteroids and/or antibiotics (72%) and no COPD exacerbations requiring hospitalisation (89%) in the 12 months prior to screening.

Tiotropium Comparator Studies

In the two 6-month active-controlled (tiotropium 18 micrograms administered once daily) studies (DB2113360 and ZEP117115), treatment with umeclidinium/vilanterol 62.5/25 micrograms demonstrated statistically significant improvements in the primary end point of trough FEV_1 compared with tiotropium at Week 24 in the first study (improvement over tiotropium by 90 ml [95% CI=39 ml to 141 ml; p<0.001]) and in the second study (improvement over tiotropium by 112 ml [95% CI=81 ml to 144 ml; p<0.001]). In study DB2113374, treatment with umeclidinium/vilanterol 62.5/25 micrograms showed a numerically greater improvement at Week 24 compared with tiotropium (improvement over tiotropium by 60 ml [95% CI=10 ml to 109 ml]).

In studies DB2113360 and ZEP117115, umeclidinium/vilanterol 62.5/25 micrograms showed statistically significant greater improvements of 74 ml [95% CI=22 ml to 125 ml; p=0.005] and 105 ml [95% CI=71 ml to 140 ml; p<0.001] respectively in change from baseline in weighted mean FEV_1 over 0-6 hours at Week 24 (secondary endpoint) compared with tiotropium. In study DB2113374, umeclidinium/vilanterol 62.5/25 micrograms showed a clinically meaningful improvement of 96 ml [95% CI=50 ml to 142 ml] in change from baseline in weighted mean FEV_1 over 0-6 hours at Week 24 compared with tiotropium.

In studies DB2113360 and DB2113374 umeclidinium/vilanterol 62.5/25 micrograms and tiotropium both improved measures of dyspnoea (TDI focal score) and health-related quality of life (SGRQ) compared with baseline. In the third active-comparator study (ZEP117115), a statistically significant improvement compared with tiotropium in the change from baseline in SGRQ total score at Week 24 was demonstrated for umeclidinium/vilanterol (-2.10 units; p=0.006). The percentage of patients receiving umeclidinium/vilanterol that responded with a reduction from baseline of ≥4 units (MCID) in SGRQ total score from this study was 53% (237/445) compared with 46% (196/430) for tiotropium.

Statistically significant improvements in rescue salbutamol use over weeks 1-24 were observed for umeclidinium/vilanterol 62.5/25 micrograms over tiotropium in studies DB2113360 (-0.7 puffs per day [95% CI=-1.2 to -0.1; p=0.022]) and ZEP117115 (-0.5 puffs per day [95% CI=-0.7 to -0.2; p<0.001]).

Throughout studies DB2113360, ZEP117115 and DB2113374, patients treated with umeclidinium/vilanterol had, on average, a greater reduction from baseline in the proportion of days when no rescue medication was needed (18.6%, 21.5% and 17.6% respectively) compared with tiotropium (11.7%, 13.3%, and 13.4% respectively; no formal statistical analysis was performed on this endpoint).

In study ZEP117115, treatment with umeclidinium/vilanterol resulted in a statistically significant 50% reduction in risk of a moderate/severe COPD exacerbation (based on analysis of time to first exacerbation) compared with tiotropium (Hazard Ratio 0.5; 95% CI: 0.3, 1.0; p=0.044) where the majority of patients reported no COPD exacerbations requiring oral/systemic corticosteroids and/or antibiotics (83%) and no COPD exacerbations requiring hospitalisation (93%) in the 12 months prior to screening.

Supportive 3 month exercise endurance studies

Exercise endurance was evaluated with the endurance shuttle walk test (ESWT) in adult COPD patients with hyperinflation (functional residual capacity [FRC] >120%) in two replicate, 12-week clinical studies.

In one study (DB2114418), treatment with umeclidinium/vilanterol 62.5/25 micrograms demonstrated a statistically significant improvement over placebo in exercise endurance time (EET) obtained 3 hours after dosing at Week 12 of 69.4 seconds (95% CI=24.5 seconds to 114.4 seconds; p=0.003). Improvement in EET compared with placebo was seen at Day 2 and was sustained at Week 6 and Week 12. In the second study (DB2114417), treatment with umeclidinium/vilanterol 62.5/25 micrograms did not show a statistically significant improvement in EET over placebo (21.9 seconds; p= 0.234).

In the first study, umeclidinium/vilanterol 62.5/25 micrograms showed a statistically significant improvement compared to placebo in change from baseline in trough FEV_1 at Week 12 of 243 ml [95% CI=202 ml to 284 ml; p<0.001] and a statistically significant improvement compared to placebo in change from baseline in lung volume measures at trough and at 3 hours post dose at Week 12 (inspiratory capacity: 237 ml and 316 ml

respectively, residual volume: -466 ml and -643 ml respectively and functional residual capacity: -351 ml and -522 ml respectively; all p<0.001). In the second study, umeclidinium/vilanterol 62.5/25 micrograms showed a clinically meaningful improvement compared to placebo in change from baseline in trough FEV_1 of 211 ml [95% CI=172 ml to 249 ml] and improvements compared to placebo in change from baseline in lung volume measures at trough and at 3 hours post dose at Week 12 (inspiratory capacity: 198 ml and 238 ml respectively, residual volume: -295 ml and -351 ml respectively and functional residual capacity: -238 ml and -302 ml respectively).

Supporting efficacy studies

In a randomised, double-blind, 52-week study (CTT116855, IMPACT), adult patients with COPD and a history of 1 or more moderate or severe exacerbations in the prior 12 months were randomised (1:2:2) to receive umeclidinium/vilanterol (UMEC/VI 62.5/25 micrograms), fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI 100/62.5/25 micrograms), or fluticasone furoate/vilanterol (FF/VI 100/25 micrograms) administered once daily. The primary endpoint was annual rate of on-treatment moderate and severe exacerbations in subjects treated with FF/UMEC/VI compared with FF/VI and UMEC/VI. The mean annual rate of exacerbations was 0.91, 1.07 and 1.21 for FF/UMEC/VI, FF/VI, and UMEC/VI respectively.

Treatment with UMEC/VI resulted in a similar risk of a moderate/severe exacerbation when compared with FF/VI (based on analysis of time to first exacerbation) (risk increase of +1.4%; Hazard Ratio:1.01; 95% CI: 0.94, 1.09; p=0.708).

Umeclidinium

In the IMPACT study, treatment with umeclidinium as a component of FF/UMEC/VI compared with FF/VI resulted in a statistically significant 15% reduction in the annual rate of on-treatment moderate/severe exacerbations (Rate Ratio: 0.85; 95% CI: 0.80, 0.90; p<0.001).

Treatment with umeclidinium as a component of FF/UMEC/VI compared with FF/VI resulted in a statistically significant 14.8% reduction in risk of a moderate/severe exacerbation (based on analysis of time to first exacerbation) (Hazard Ratio 0.85; 95% CI: 0.80, 0.91; p<0.001).

Vilanterol

In a placebo controlled study (HZC113782, SUMMIT), where patients with COPD were treated for up to 4 years (mean 1.7 years), the majority of patients reported no COPD exacerbations requiring oral/systemic corticosteroids and/or antibiotics (68%) and no COPD exacerbations requiring hospitalisation (87%) in the 12 months prior to screening. Treatment with vilanterol 25 micrograms resulted in a statistically significant 10% reduction in the annual rate of on-treatment moderate/severe exacerbations compared with placebo (Rate Ratio: 0.90; 95% CI: 0.82, 0.98; p=0.017). Vilanterol as a component of fluticasone furoate/vilanterol (FF/VI 100/25 micrograms) compared with fluticasone furoate (FF 100 micrograms) resulted in a statistically significant 19% reduction in the annual rate of on-treatment moderate/severe exacerbations (Rate Ratio: 0.81; 95% CI: 0.74, 0.88; p<0.001).

These findings were supported by a statistically significant 8.9% reduction in risk of a moderate/severe exacerbation (based on analysis of time to first exacerbation) for vilanterol compared with placebo (Hazard Ratio: 0.91; 95% CI: 0.84, 0.99; p=0.023) and by a statistically significant 18.2% reduction in risk of a moderate/severe exacerbation (based on analysis of time to first exacerbation) for vilanterol as a component of FF/VI compared with FF (Hazard Ratio: 0.82; 95% CI: 0.75, 0.89; p<0.001).

5.2 Pharmacokinetic properties

When umeclidinium and vilanterol were administered in combination by the inhaled route, the pharmacokinetics of each component was similar to those observed when each active substance was administered separately (see section 5.2. Pharmacokinetic properties – *Biotransformation* and section 4.5. Interaction with other medicines and other forms of interaction). For pharmacokinetic purposes each component can therefore be considered separately.

Absorption

Umeclidinium

Following inhaled administration of umeclidinium in healthy volunteers, C_{max} occurred at 5 to 15 minutes. The absolute bioavailability of inhaled umeclidinium was on average 13% of the dose, with negligible contribution from oral absorption. Following repeat dosing of inhaled umeclidinium, steady state was achieved within 7 to 10 days with 1.5 to 2-fold accumulation.

Vilanterol

Following inhaled administration of vilanterol in healthy volunteers, C_{max} occurred at 5 to 15 minutes. The absolute bioavailability of inhaled vilanterol was 27%, with negligible contribution from oral absorption. Following repeat dosing of inhaled vilanterol, steady state was achieved within 6 days with up to 2.4-fold accumulation.

Distribution

Umeclidinium

Following intravenous administration to healthy subjects, the mean volume of distribution was 86 litres. In vitro plasma protein binding in human plasma was on average 89%.

Vilanterol

Following intravenous administration to healthy volunteers, the mean volume of distribution at steady state was 165 litres. In vitro plasma protein binding in human plasma was on average 94%.

Biotransformation

Umeclidinium

In vitro studies showed that umeclidinium is metabolised principally by the enzyme P450 CYP2D6 and is a substrate for the P-glycoprotein (P-gp) transporter. The primary metabolic routes for umeclidinium are oxidative (hydroxylation, O-dealkylation) followed by conjugation (glucuronidation, etc), resulting in a range of metabolites with either reduced pharmacological activity or for which the pharmacological activity has not been established. Systemic exposure to the metabolites is low.

Vilanterol

In vitro studies showed that vilanterol is metabolised principally via CYP3A4 and is a substrate for the P-gp transporter. The primary metabolic routes are O-dealkylation to a range of metabolites with significantly reduced $beta_1$- and $beta_2$- agonist activity. Plasma metabolic profiles following oral administration of vilanterol in a human radiolabel study were consistent with high first-pass metabolism. Systemic exposure to the metabolites is low.

Elimination

Umeclidinium

Plasma clearance following intravenous administration was 151 litres/hour. Following intravenous administration, approximately 58% of the administered radiolabelled dose (or

73% of the recovered radioactivity) was excreted in faeces by 192 hours post-dose. Urinary elimination accounted for 22% of the administered radiolabelled dose by 168 hours (27% of recovered radioactivity). The excretion of the drug-related material in the faeces following intravenous dosing indicated secretion into the bile. Following oral administration to healthy male subjects, total radioactivity was excreted primarily in faeces (92% of the administered radiolabelled dose or 99% of the recovered radioactivity) by 168 hours post-dose. Less than 1% of the orally administered dose (1% of recovered radioactivity) was excreted in urine, suggesting negligible absorption following oral administration. Umeclidinium bromide plasma elimination half-life following inhaled dosing for 10 days averaged 19 hours, with 3% to 4% drug excreted unchanged in urine at steady-state.

Vilanterol

Plasma clearance of vilanterol following intravenous administration was 108 litres/hour. Following oral administration of radiolabelled vilanterol, mass balance showed 70% of the radiolabel in urine and 30% in faeces. Primary elimination of vilanterol was by metabolism followed by excretion of metabolites in urine and faeces. Vilanterol plasma elimination half-life following inhaled dosing for 10 days averaged 11 hours.

Special patient populations

Elderly

A population pharmacokinetic analysis showed that pharmacokinetics of umeclidinium and vilanterol were similar between COPD patients 65 years and older and those younger than 65 years of age.

Renal impairment

Subjects with severe renal impairment showed no evidence of an increase in systemic exposure to either umeclidinium or vilanterol (C_{max} and AUC), and no evidence of altered protein binding between subjects with severe renal impairment and healthy volunteers.

Hepatic impairment

Subjects with moderate hepatic impairment showed no evidence of an increase in systemic exposure to either umeclidinium or vilanterol (C_{max} and AUC), and no evidence of altered protein binding between subjects with moderate hepatic impairment and healthy volunteers. Umeclidinium/vilanterol has not been evaluated in subjects with severe hepatic impairment.

Other patient characteristics

A population pharmacokinetic analysis showed that no dose adjustment is required for umeclidinium or vilanterol trifenatate based on the effect of age, race, gender, inhaled corticosteroid use, or weight. A study in CYP2D6 poor metabolisers showed no evidence of a clinically significant effect of CYP2D6 genetic polymorphism on systemic exposure to umeclidinium.

5.3 Preclinical safety data

Genotoxicity

Umeclidinium was not genotoxic in a standard battery of studies.

Genetic toxicity studies indicate vilanterol trifenatate does not represent a genotoxic hazard to humans.

Carcinogenicity

Umeclidinium was not carcinogenic in lifetime inhalation studies in mice or rats at exposures ≥ 26 or ≥ 22-fold, times the human clinical exposure of umeclidinium 62.5 micrograms, based on AUC, respectively.

Consistent with findings for other beta$_2$-agonists, in lifetime inhalation studies vilanterol trifenatate caused proliferative effects in the female rat and mouse reproductive tract and in the rat pituitary gland. There was no increase in tumour incidence in rats or mice at exposures 0.5- or 13-fold, times the human clinical exposure of vilanterol 25 micrograms based on AUC, respectively.

Effect on Laboratory Tests

Interactions with laboratory tests have not been established.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Magnesium stearate

Lactose monohydrate (which contains milk proteins)

6.2 Incompatibilities

None reported.

6.3 Shelf life

2 years

In-use shelf-life

6 weeks

Write the date the inhaler should be discarded on the label in the space provided. The date should be added as soon as the inhaler has been removed from the tray.

6.4 Special precautions for storage

Store below 30°C.

If stored in the refrigerator, allow the inhaler to return to room temperature for at least an hour before use.

6.5 Nature and contents of the container

The plastic Ellipta inhaler consists of a light grey body, a red mouthpiece cover and a dose counter, packed into a foil laminate tray containing a desiccant sachet. The tray is sealed with a peelable foil lid.

The inhaler contains two strips of 7 or 30 regularly distributed blisters, each containing a white powder.

Packs containing a single inhaler providing either 7 or 30 doses.

Not all strengths and pack sizes may be distributed in New Zealand.

6.6 Special precautions for disposal and other handling

Disposal

Any unused medicine should be disposed of in accordance with local requirements.

Instructions for Handling

The Ellipta inhaler is provided in a foil laminate tray containing a desiccant sachet. The tray provides moisture protection and should only be opened when you are ready to use it for the first time. Once opened the desiccant sachet should be discarded.

Only open the Ellipta inhaler cover when you are ready to take a dose.

If you open and close the cover of the Ellipta inhaler without inhaling the medicine, you will lose the dose. The dose will be securely held inside the inhaler, but it will be no longer available. It is not possible to accidently take extra medicine or a double dose in one inhalation.

When you first use the Ellipta inhaler you do not need to check that it is working properly, and you do not need to prepare it for use in any special way.

Your device may contain either 30 or 7 starting doses.

Important

The dose-counter indicates the number of doses left. Patients should consider getting a replacement when the counter shows the number 05. When the counter shows a full solid red background it must be replaced.

7. MEDICINE SCHEDULE

Prescription Only Medicine

8. SPONSOR

GlaxoSmithKline NZ Limited
Private Bag 106600
Downtown
Auckland
New Zealand

Phone: (09) 367 2900
Facsimile (09) 367 2910

9. DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine:
20 March 2014.

10. DATE OF REVISION OF THE TEXT

7 March 2023

Summary table of changes

Section changed	Summary of new information
4.8	Update to post-marketing data to include headache

Version 10.0